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David Wallach

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EXAMINER

WEN, SHARON X

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/573,136	Applicant(s) WALLACH ET AL.	
	Examiner SHARON WEN	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 October 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19, 26-36 and 45-61 is/are pending in the application.
- 4a) Of the above claim(s) 26-36 and 45-61 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment, filed 10/13/2009, has been entered.

Claims 20-25, 37-44 and 62-63 have been canceled.

Claims 1-19, 26-36 and 45-61 are pending.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 10/13/2009 is acknowledged. The traversal is on the ground(s) that Rothe et al. (U.S. Patent 5,854,003) does not destroy the special technical feature of the instant claims because Rothe et al. taught a mutant NIK polypeptide containing a substitution at position 25 compared to the NIK sequence of the instant application. This is not found persuasive for the following reasons:

Rothe et al. taught immunizing rabbit with the NIK polypeptide. Even though Rothe's NIK polypeptide contains a substitution at position 25, one of ordinary skill in the art would have recognized that the polyclonal antiserum generated by immunizing rabbits with Rothe's NIK would necessarily bind to at least a portion of the amino acid sequence containing Thr-559 under the broadest reasonable interpretation because polyclonal antibodies are known to bind multiple epitopes.

The requirement is still deemed proper and is therefore made FINAL.

Claims 26-36 and 45-61 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention/species, there being no allowable generic or linking claim.

Claims 1-19 are currently under examination as they read on an anti-NIK antibody that binds SEQ ID NO: 5, 6, or 3.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is drawn to a pharmaceutical composition comprising the antibody or the antibody fragment of claim 14 that is derived from murine origin. However, claim 14 recites that the antibody is a human antibody. Therefore, claim 17 is indefinite as to whether the antibody or the antibody fragment is from murine origin or human.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibody fragment selected from the group consisting of a single chain Fv, an Fab, and Fab' and an F(ab')₂, does not reasonably provide enablement for **a CDR**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The breadth of the instant claims encompass an antigen-binding antibody fragment in which **fewer than all of the six CDRs** found in the heavy plus light chain pair that forms the binding region of a referenced antibody are defined. Therefore, the following grounds of rejection have been set forth.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is

characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. J. Mol. Biol. (1996) 262, 732-745, analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). Pascalis et al. (The Journal of Immunology (2002) 169, 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, *some residues in all 6 CDRs were used for the constructs* (see page 3080, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (BBRC 2003, 307:198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, *clearly other CDRs play an important role in the recognition process* (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Vajdos et al. (J. Mol. Biol. (2002) 320, 415-428), additionally state

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that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.). Chen et al. (J. Mol. Bio. (1999) 293, 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. (J. Mol. Biol. (1999) 294, 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation. Padlan et al. (PNAS 1989, 86:5938-5942) described the crystal structure of an antibody-lysozyme complex where all 6 CDRs contribute at least one residue to binding and one residue in the framework is also in contact with antigen. Lastly, Lamminmaki et al. (JBC 2001, 276:36687-36694) describe the crystal structure of an anti-estradiol antibody in complex with estradiol where, although CDR3 of VH plays a prominent roll, all CDRs in the light chain make direct contact with antigen (even CDR2 of VL, which is rarely directly involved in hapten binding).

Thus the state of the art recognized that it would be highly unpredictable that an antibody or the antigen-binding fragment thereof comprising less than all six CDRs from both the VH and VL regions with a desired specificity would bind the same antigen. Thus the minimal structure which provides the function of NIK-binding appears to include six CDRs (three in the heavy chain variable region and three in the light chain variable region) from the same antibody.

The instant disclosure enabled the antibodies with both heavy and light chain variable regions for binding NIK peptides. For example, the antibody generated in Example 1 of the instant specification comprises both heavy and light chain variable regions as set forth and the respective 6 CDRs. The specification as filed did not provide any evidence showing any antibody with fewer than all 6 CDRs can bind NIK.

Without sufficient guidance, and in view of the unpredictability of the art, it would require undue experimentation of the skilled artisan to make or use the claimed antibodies or antigen-binding fragments thereof with less than all six CDRs in order to bind NIK and detect NIK by Western or ELISA as commensurate in scope with the instant specification.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claims 1-12, 14, 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds the amino acid sequence set forth in SEQ ID NO: 5, 6 or 3, does not reasonably provide enablement for an antibody that binds **any** amino acid sequence or **any** portion of the amino acid sequences set forth in SEQ ID NO: 5, 6 or 3 for detecting NIK **or a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Under the broadest reasonable interpretation, the present claims are broadly drawn to antibodies that bind to an amino acid sequence or a portion of the amino acid sequence which reads on variants or fragments of the peptides with any minimal consecutive 2 amino acids. However, other than the antibodies binding to the amino acid sequence set forth in SEQ ID NOs: 5, 6 or 3, there does not appear to be an actual reduction to practice of an antibody that binds other species of the genus encompassing the variants of SEQ ID NOs: 5, 6 or 3; nor is there a complete or partial structure of an antibody capable of binding all the species of the above mentioned genus in detailed drawing or through a structural chemical formula, e.g., sequence of the antibody.

Furthermore, a skilled artisan is well aware that such antibodies binding the amino acid sequences of SEQ ID NOs: 5, 6 or 3 would not reasonably be expected to be reactive with all members of the genus encompassing all the variants of the peptides. For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991; see entire document) disclosed that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody. Further, Li et al. (PNAS 77: 3211-3214, 1980; see entire document) disclosed that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Moreover, for instance, Houghten et al. (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al. state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool."

Given that the instant specification disclosed that the claimed antibody is used for detection of NIK or a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof. One of skill in the art would not be able to use the antibody that binds to SEQ ID NO: 5, 6 or 3 to measure all the variants of SEQ ID NO: 5, 6 or 3 or detect NIK or a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof, because, as the state of the art discussed above, the antibody that binds SEQ ID NO: 5, 6 or 3 would not be able to bind to all the variants of the peptides or NIK.

Therefore, the specification, as-filed, provided insufficient guidance to lead a person of skill in the art to use the claimed antibodies that binds SEQ ID NO: 5, 6 or 3 to measure all the variants of SEQ ID NO: 5, 6 or 3 commensurate in scope of the instant disclosure.

Reasonable correlation must exist between the scope of the claims and scope of

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the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant is invited to amend the claims to recite "the amino acid sequence of SEQ ID NO: 5, 6 or 3" and avoid the recitation of "a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof" in order to obviate this rejection.

Claims 11 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a biological deposit rejection.*

It appears that NIK-P4 30.12 hybridoma clone is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line. See 37 CFR 1.801-1.809.

It appears that the above mentioned hybridoma clone has been deposited with CNCM under the Budapest Treaty. However, in addition to the conditions under the Budapest Treaty, Applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Applicant's assurance will obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6-10, 12, 14-16 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Schreiber et al. (US 6,822,138 B1, see entire document).

Schreiber taught a polyclonal antibody that binds specifically to NIK (see e.g., column 15, paragraph 4) and a pharmaceutical composition comprising the antibody as a modulator of NIK and a pharmaceutically acceptable carrier (see column 18, lines 41-49 and column 27, lines 32-43).

Although Schreiber et al. did not teach the polyclonal antibody to NIK to bind specifically to a portion of NIK comprising phosphorylated threonine 559, given that polyclonal antibodies are known to bind multiple epitopes on one antigen, the prior art polyclonal antibody raised against NIK would necessarily bind to the epitopes comprising threonine 559. Therefore, the prior art antibody would be capable of specifically detecting phosphorylated NIK or a specific portion thereof by Western, ELISA or immunoprecipitation. Furthermore, the prior art antibody would also be able to regulate a biochemical activity of NIK because it is a polyclonal antibody that binds multiple epitopes on NIK which would the kinase activation site of NIK, thereby inhibiting the activity of NIK.

Since the Office does not have a laboratory to test the prior art polyclonal antibody, it is Applicant's burden to provide objective evidence showing that Schreiber's polyclonal antibody raised against NIK does not bind to portions of NIK comprising phosphorylated threonine 559.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-10, 12, 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schreiber et al. (US 6,822,138 B1) in view of Lin et al. (Mol Cell Biol. 1998, 18(10):5899–5907) and Campbell (*Monoclonal Antibody Technology*, 1984, Chapter 1, pages 1-32), Green (*JIM* 1999 231:11-23) and Owens et al. (*JIM*, 1994, 168:149-165).

The teaching by Schreiber et al. has been discussed supra.

Schreiber et al. did not teach the antibody to bind specifically to the portion of NIK comprising a phosphorylated threonine 559 as set forth in SEQ ID NO: 6 or 3. However, it would have been obvious to one of ordinary skill in the art, at the time of the invention was made, to make an antibody specifically to the region comprising phosphorylated threonine 559 because the region containing threonine 559 was known to be the activation loop of NIK as taught by Lin et al. (see entire document). In particular, Lin taught that substitution of Thr-559 with an alanine within the activation loop abolishes NIK activity and its ability to phosphorylate and activate IKK α ; and that a NIK-T559A mutant also dominantly interferes with TNF- α induction of NF- κ B (see e.g., Results and Discussion). Given such knowledge, one of ordinary skill in the art would have been reasonably expected to make an antibody that would bind to a region containing Thr-559 in the activation loop to block the site for activation. Furthermore, one of ordinary skill in the art would have been motivated to make such antibody in view of Campbell's teaching in that it is customary for any group working on a macromolecule to make monoclonal antibodies to it, sometimes even without a clear objective for their application (see Campbell, page 29, last paragraph). Given that Lin et al. taught that

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the activation loop of the NIK contained Thr-559 and that the phosphorylation of Thr-559 is critical in the regulation of NIK function (see Introduction), one of ordinary skill in the art would have been motivated to make an antibody against the activation loop of the NIK which contains the phosphorylated Thr-559 to study the molecule using common assays such as Western, ELISA and immunoprecipitation.

With respect to "human antibody", the following is noted.

Schreiber et al. did not teach that the anti-NIK antibody is a human antibody. However it have been obvious to one of skill in the art at the time of the invention was made to make a human antibody against NIK because it was well-known in the art to make a human antibody as evidenced by Green (see entire document).

In particular, Green taught that XenoMouse strains of mice produced human monoclonal IgG antibodies (see, e.g., page 13-16, Section 2). Furthermore, Green taught that immunization of XenoMouse mice with human antigen *routinely* results in a robust secondary immune response, which can be ultimately captured as a large panel of antigen-specific fully human IgG mAb of sub-nanomolar affinity (see, e.g., Abstract). More over, one of ordinary skill in the art would also have been motivated to make the human anti-NIK antibodies because Green taught that monoclonal antibodies from XenoMouse animals have been shown to have therapeutic potential both in vitro and vivo (see, e.g., Abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to make the human anti-NIK antibody given that both the starting material, NIK antigen and the method of making human antibody with the antigen were both well-known in the art at the time of the invention was made.

With regard to "humanized or chimeric antibody or antibody fragments", the following is noted.

Although Schreiber did not teach the antibody to be humanized or chimeric, it would have been obvious to one of ordinary skill in the art at the time of the invention

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was made to generate a chimeric or humanized antibody against NIK because it is well-known in the art to make chimeric or humanized antibodies as evidenced by Owens et al. (see entire document, in particular, see pages 150-155).

In particular, Owens et al. taught the methods of humanizing rodent monoclonal antibodies by making human chimeric and human CDR-grafted antibodies from rodent monoclonal antibodies (see pages 150-155). Furthermore, Owen also taught the construction of antibody fragments such as Fv and scFv (see page 155).

One of ordinary skill in the art would have been motivated to make a chimeric or humanized antibody against NIK and the antibody fragments as taught by Schreiber et al. because antibodies can be used for therapeutic purposes and that making a rodent monoclonal antibody chimeric or humanized is advantageous to the rodent monoclonal antibody for human diagnosis or therapy as taught by Owens (see Introduction). Moreover, using antibody fragment has the advantage of faster clearance from the body. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to make an antibody that binds and antagonizes NIK wherein the antibody is chimeric or humanized, as well as an antibody fragment.

Given the above discussion, the invention, as a whole, was *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON WEN whose telephone number is (571)270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571)272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sharon Wen/
Examiner, Art Unit 1644
December 17, 2009